TITLE: Treatments for Constipation: A Review of Systematic Reviews

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CONTEXT AND POLICY ISSUES

Constipation has many definitions and is often described differently depending on the population queried. Physicians may define constipation as a reduction in the frequency of bowel movements to fewer than three times per week while patients identify more with the symptoms associated with constipation such as difficulty passing stool, hard stool consistency, feelings of abdominal cramping, and feelings of incomplete stool passage.[1] Causes of constipation may be primary (idiopathic) or secondary to other factors such as diet, medication, or medical conditions.[2] Constipation can affect anyone as a minor annoyance but up to a quarter of the population experiences it chronically or severely.[2] It can substantially affect quality of life and be debilitating.[2] It is estimated that between 2% to 27% of the population are affected depending upon the definition of constipation used.[1]

Several treatment options are available and include dietary or bulking agents, osmotic or stimulant laxatives, stool softeners, and 5-HT4 agonists.[1-3] Bulking agents include soluble fibre (i.e. psyllium, ispaghula) and insoluble fibre (i.e. wheat bran), which, when taken with water, increase stool bulk and stool frequency.[4] Osmotic laxatives (i.e. lactulose, polyethylene glycol [PEG], macrogol, milk of magnesia), are poorly absorbed by the gut and act as hyperosmolar agents, increasing the water content of stool and making the stool softer and easier to pass.[5] Stimulant laxatives (i.e. sennosides, bisacodyl, sodium picosulfate) act on the intestinal mucosa, increasing water and electrolyte secretion and stimulating peristalsis.[5] Stool softeners (i.e. docusate sodium or calcium) are thought to facilitate the mixing of aqueous and fatty substances and thereby soften the stool.[6] The 5-HT4 agonists (i.e. prucalopride) stimulate peristalsis which increases colonic motility in individuals with non-neurogenic causes of constipation.[3]

Considering the different causes and patient populations that may experience constipation, there are questions with regards to the efficacy and safety of the treatments available. A recent Rapid Review concluded there was a paucity of good quality of evidence to support the use of stool softeners for the management or prevention of constipation in adults in a hospital or long-term care setting.[7] Docusate appeared to be no more effective than placebo for increasing stool

frequency or softening stools and did not lessen symptoms associated with constipation.[7] The purpose of this report is to review the available evidence for the safety and efficacy of stool softeners, laxatives, bulking agents and 5-HT4 agonists for the management of constipation in adults and children.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of stool softeners for constipation?
2. What is the clinical effectiveness of laxatives for constipation?
3. What is the clinical effectiveness of bulking agents for constipation?
4. What is the clinical effectiveness of 5-HT4 agonists for constipation?

KEY FINDINGS

In adults and children with chronic constipation, polyethylene glycol (PEG), increased the frequency of stools relative to placebo, lactulose and milk of magnesia. Stool frequency was also increased in adults treated with prucalopride versus placebo. Laxatives and prucalopride may increase the risk of diarrhea. No conclusions can be drawn with regards to stool softeners or bulking agents. The available studies were generally of lower methodological quality with limited data available for many treatment comparisons or for safety.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 10), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, and meta-analyses. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 2009 and October 19, 2014.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients (any age) with constipation
Intervention	Stool softeners, stimulant laxatives, osmotic laxatives, 5-HT4 agonists, bulking agents
Comparator	Placebo or no treatment

	Any active comparator
Outcomes	Clinical effectiveness, safety
Study Designs	Systematic reviews, meta-analyses, health technology assessments

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria, if they were duplicate publications, or were published prior to 2009.

Critical Appraisal of Individual Studies

The AMSTAR tool was used to guide the critical appraisal of the methodological quality of the systematic reviewes included in this report.[8] Emphasis was placed on the methods used to conduct the literature search, study selection, quality assessment, data extraction and data summarization. A numeric score was not provided; instead the strengths and limitations of each study were described narratively,

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 194 citations were identified in the literature search. Following screening of titles and abstracts, 164 citations were excluded and 30 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, 19 publications were excluded for various reasons, while 12 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

A summary of the systematic review characteristics is listed in Appendix 2.

Twelve systematic reviews met the inclusion criteria.[3-6,9-16] Seven reviews focused on patients with chronic idopathic constipation in children,[5,9] adults,[4,11-13] or both.[10] The remaining reviews included adults with constipation associated with other disorders including postpartum constipation,[14] palliative care,[16] opioid induced constipation,[6,15] or patients with central neurological diseases and fecal incontinence or constipation.[3]

The treatments included in the systematic reviews were: stool softeners (3 reviews), laxatives (9), bulking agents (4), 5-HT4 agonists (4), and other treatments, such as surgical, educational or dietary modifications, or pharmaceutical agents that were not of interest in this report (5 reviews). The comparators were placebo or no treatment,[4,13] another active treatment,[6,9,10] or either placebo or active control.[3,5,11,12,14-16]

The outcomes reported varied across the studies. Stool frequency, constipation-related symptoms, success of therapy, need for other treatments, quality of life and adverse events were reported in the reviews. Some reviews conducted meta-analyses and pooled data from studies reporting similar outcome measures.

All trials screened for and included relevant randomized controlled trials (RCTs), and two reviews also included quasi-randomized or comparative prospective studies.[3,9] The number of studies included in each review ranged from 0 to 21 RCTs. Of note, this Rapid Review focused on data for the interventions and comparators listed in Table 1, which may be a subset of the data included in some systematic reviews.

Summary of Critical Appraisal

A summary of the critical appraisal is listed in Appendix 3.

Overall, the systematic reviews were of high methodological quality. The authors conducted literature searches of multiple electronic databases, reviewed reference lists and many hand searched abstracts. Limitations included the exclusion of non-English studies[9] or unpublished studies,[12] and in seven reviews it was not clear if the authors conducted a comprehensive search for unpublished data.[3-5,10-13] All but one review[12] reported that studies were screened for inclusion, appraised for validity, and extracted independently by two researchers. The review by Belsey et al.[12] did not clearly report selection and extraction methods. One review evaluated efficacy of treatments but not potential adverse effects.[10] Four reviews did not evaluate the risk of publication bias.[3,4,11,12] Potential conflicts of interest with pharmaceutical industry were disclosed in four reviews.[6,11,12,16]

Summary of Findings

A summary of the systematic review findings are listed in Appendix 4 with efficacy data reported in Tables 2 to 4, and adverse events in Table 5. Data for drugs no longer available in Canada (e.g. cisapride, tegaserod), and for dietary sources of fibre (e.g. rye bread) were not summarized in this report.

Efficacy

Stool softeners

Although stool softeners were an intervention of interest in three systematic reviews, none of the studies included in these reviews identified studies evaluating these agents.[3,6,14]

Laxatives

Data on the efficacy of laxatives compared with placebo was available from four systematic reviews.[3,5,12,13] Some of the same studies for prucalopride[11,13] and PEG[11,13] were included in more than one systematic review.

The systematic review by Ford et al.[13] pooled data for laxatives (lactulose, PEG, bisacodyl and sodium picosulfate) compared to placebo. In adults with chronic idopathic constipation, the mean number of stools per week was statistically significantly higher for laxatives versus placebo [mean difference (MD) 2.55 stools per week; 95% confidence interval (CI), 1.53 to 3.57]

based on data from six RCTs. Heterogeneity (i.e., between study variability) was high (I^2 = 100%). Fewer patients who received laxatives failed to respond to therapy compared with placebo [relative risk (RR) 0.52; 95% CI, 0.46 to 0.60), 7 RCTs, I^2 = 42%].[13] The findings were similar when the data for osmotic and stimulant laxatives were pooled separately.[13]

In children with functional constipation, polyethylene glycol (PEG) was associated with a statistically significant increase in the mean number of stools per week compared to placebo (MD 2.61; 95% CI, 1.15 to 4.08) based on pooled data from two RCTs rated as low quality evidence.[5] Similar efficacy was reported in adults with non-organic constipation. PEG statistically significantly increased the number of stools by 1.98 stools per week compared to placebo (95% CI, 1.16 to 2.81, 10 RCTs).[12] Heterogeneity was present in both analyses (I^2 58% and 82%, respectively).

In one RCT, those who received eight weeks of macrogol electrolyte solution showed a statistically significant increase in stool frequency compared to placebo among adults with Parkinson's disease and constipation (MD 2.90; 95% CI, 1.48 to 4.32).[3] Patients on macrogol were less likely to show lack of response to treatment than those who received placebo (RR 0.29; 95% CI, 0.11 to 0.72).[3]

Five systematic reviews reported data comparing the efficacy of laxatives versus another active treatment.[5,9,10,12,16] Some of the same studies were included in more than one systematic review.[5,9,10,12]

In children with chronic functional constipation, stool frequency was not statistically significantly different when pooled data for PEG was compared to non-PEG laxatives (7 RCTs, I^2 = 89%).[9] Comparisons between specific agents showed that stool frequency was statistically significantly higher for PEG versus milk of magnesia (MD 0.69 stools per week; 95% CI, 0.48 to 0.89; 3 RCTs, I^2 = 0%, rated as low quality evidence).[5] No statistically significant difference in stool frequency was detected between PEG and liquid paraffin or enemas, and for lactulose versus senna or lactitol.[5] Low quality evidence showed that stool frequency was statistically significantly higher for liquid paraffin versus lactulose (MD 4.94 stools per week; 95% CI, 4.28 to 5.61; 2 RCTs, I^2 = 0%).[5]

In children with functional constipation, PEG statistically significantly increased stool frequency on average by 1.09 stools per week (95% CI, 0.02 to 2.17) compared to lactulose (4 RCTs, I^2 = 70%, rated as very low qualtiy evidence).[5] The results were similar for PEG versus lactulose when data from children and adults were pooled (MD 0.65; 95% CI, 0.15 to 1.15; 5 RCTs, I^2 = 77%)[10] and for adults only (MD 1.01; 95% CI, 0.41 to 1.62; 7 RCTs, I^2 = 54%).[12] Of note, some RCTs comparing PEG and lactulose were included in more than one pooled analysis.[5,10,12]

In children with functional constipation, disimpaction was more likely to be successful with PEG versus non-PEG laxatives,[9] but no significant difference was found between PEG and enemas.[5] In adults and children with chronic constipation, those who received PEG were less likely to require additional therapy compared to those who recevied lactulose.[5,10]

In adults with chronic non-organic constipation, PEG with electrolytes demonstrated similary efficacy (i.e., was non-inferior) to PEG without electrolytes in terms of stool frequency in one RCT.[12] Among palliative care patients, no statistically significant difference in stool frequency was detected for senna versus lactulose, or for magnesium hydroxide plus liquid paraffin versus senna plus lactulose (1 RCT for each comparison).[16]

Bulk-forming agents

Data comparing bulk-forming laxatives to placeo were available from two systematic reviews.[3,4] In adults with chronic idopathic constipation, psyllium increased the mean number of stools per week by 0.9 stools, compared to no change in the placebo group ($P < 0.05$) in one eight week trial.[4] A second trial found that adults with chronic constipation who received two weeks of psyllium were more likely to report nomalization of bowel function than those who received placebo (87% versus 30%, $P < 0.001$).[4] A third two week study found that 87% patients allocated to psyllium reported improvement in symptoms compared to 47% those who received placebo.[4] One low quality study in 7 people with Parkinson's disease showed an increase of 2.2 bowel motions per week (95% CI, 1.4 to 3.0) after eight weeks of psyllium compared to placebo.[3]

In children with functional constipation, dietary fibre showed no difference in stool frequency compared to lactulose (mean 7 versus 6 stools per week, respectively; $P = 0.48$) in one RCT.[5] PEG was superior to ispaghula in two RCTs that enrolled adults with chronic non-organic constipation.[12] The mean difference between groups was 2.78 ($P < 0.001$) and 1.09 ($P < 0.05$) stools per week in each study.[12]

5-HT4 agonists

Data comparing 5-HT4 agonists to placebo were reported in three systematic reviews.[3,11,15] Shin et al.[11] pooled data from 11 RCTs and found that adults with chronic constipation who received 5-HT4 agonists (prucalopride, velusetrag or naronapride) were statistically significantly more likely to report three or more spontaneous complete bowel movements per week (SCBM) (RR 1.85; 95% CI, 1.23 to 2.79) and were more likely to have an improvement of ≥ 1 SCBM per week (RR 1.57; 95% CI, 1.19 to 2.06) than those who received placebo ($I^2 = 89\%$).[11] Moreover, those who received 5-HT4 agonists were significantly more likely to report an improvement of one or more point on the Patient Assessment of Constipation Symptom questionaire and the satisfaction subscale of the Patient Assessment of Constipation Quality of Life questionaire (6 RCTs, I^2 83% and 91%). These scales measure constipation-related symptoms and quality of life, and are scored from 0 to 4.[11] Ford et al.[13] pooled data from seven RCTs (six of which were included in the review by Shin et al.[11]) and found those who received prucalopride were statistically significantly less likey to fail to respond to therapy than those who received placebo (RR 0.82; 95% CI, 0.76 to 0.88; $I^2 = 60\%$).

No statistically significant difference was detected between prucalopride and placebo in the proportion of patients with an increase of one or more SCBM per week, in one RCT that enrolled patients with opiod induced constipation.[15] A small, statistically significant, increase in the median number of weekly bowel movements (0.6; 95% CI 0.2 to 1.2), from baseline to week four, was found in one RCT of patients with spinal cord injury and constipation who received prucalopride 2 mg/day.[3] Another RCT in 11 patients with multiple sclerosis reported that constipation severity improved among those who received prucalopride (no details available).[3]

Adverse events

Most systematic reviews reported gastrointestinal adverse events, such as diarrhea, nausea, abdominal pain, cramping, bloating and flatulence, with therapies for constipation.[3-5,9,11-13,15,16] Ford et al.[13] reported that laxatives were associated with an increased risk of any adverse event (RR 1.94; 95% CI, 1.52 to 2.47; 1 RCT), or diarrhea (RR 13.75; 95% CI, 2.82 to 67.14; 2 RCTs),

but not abdominal pain or headache, versus placebo. Prucalopride was associated with a statistically significant increased risk of any adverse event, headache, nausea and diarrhea, compared with placebo.[11,13] The relative incidence of adverse events was difficult to determine using the data available from other reviews.

The occurrence of serious adverse events was reported in three reviews,[5,12,13] and based on these limited data, serious adverse events appear to be infrequent.

Limitations

Although the systematic reviews were of high methodological quality, they were limited by the quality of the included studies. The majority of RCTs were rated as low or moderate quality by the review authors, with important limitations related to randomization, allocation concealment and blinding. Furthermore, studies were generally a few weeks in duration and many enrolled a limited sample size. Substantial heterogeneity between trials was detected in pooled analyses with I^2 values exceeding 50% for several comparisons. This may be explained in part due to differences in how constipation and outcomes were defined across RCTs. No data were available for stool softeners, or for prucalopride compared to another treatment. Most comparisons between active agents were limited to one or two RCTs. The greatest volume of studies were available for PEG or lactulose, however overall, this evidence was rated as low quality in one systematic review that used the GRADE system.[5] Data on advese events were sparse and reporting incomplete, and one systematic review provided no information on treatment-related harms.[10]

For some treatment comparisons, the same studies were included in more than one systematic review, thus the volume or strength of evidence available may appear to be inflated. Given the broad scope and volume of studies included in this report, it was not possible to examine the characteristics and quality of individual RCTs included in the systematic reviews, thus assessments made by the review authors were relied on.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

There is a lack of RCT evidence to support the use of stool softeners.

In adults and children with chronic constipation, polyethylene glycol (PEG), increased the frequency of stools on average by 2 to 3 stools per week, relative to placebo. PEG may increase stool frequency compared to lactulose or milk of magnesia, however the magnitude of difference is approximately one stool per week, and the evidence was rated as low quality. No conclusions can be drawn for other laxatives.

Limited data were available for bulk-forming laxatives and although these data were suggestive of a benefit with psyllium compared to placebo, no conclusions can be drawn.

In adults with chronic constipation, prucalopride increased stool frequency and improved constipation-related symptoms compared with placebo. No data were available comparing prucalopride to other therapies for constipation.

The data suggests that diarrhea occurres more frequently with laxatives and prucalopride compared with placebo. No conclusions can be drawn with regards to the relative safety of one treatment versus another.

The systematic reviews were limited by the quality of the included systematic reviews, the majority of which were rated as low or moderate methodologic quality. Substantial between-study heterogeneity was detected for most treatment comparisons with data suitable for meta-analysis.

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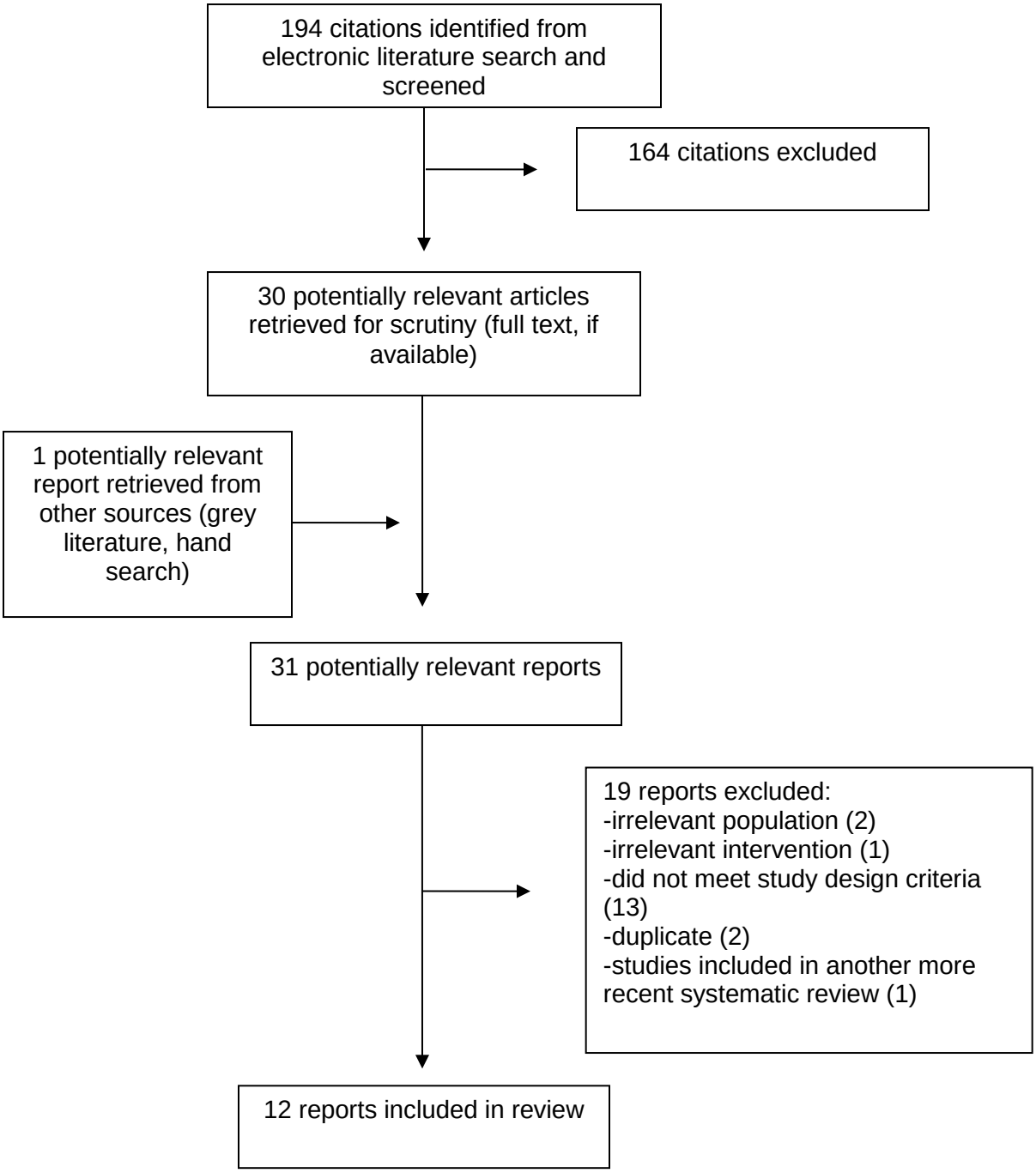
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Systematic Reviews

Author, year	Population	Adults	Children	**Interventions**	Stool softeners	Laxatives	Bulking agents	5-HT4 agonists	Other	Treatment comparisons	**Study designs**	RCTs	Other designs	Total studies included	Literature search date
Chronic constipation															
Chen 2014[9]	childhood chronic or functional constipation		x			x	x			PEG versus lactulose, milk of magnesia, mineral oil, acacia fibre, psyllium fibre or fructose		x	x	10	2014
Gordon 2012[5]	childhood functional constipation		x			x				osmotic or stimulant laxatives versus placebo or another intervention		x		18	2012
Lee-Robichaud 2010[10]	chronic constipation	x	x			x				PEG versus lactulose		x		10	2008
Shin 2014[11]	chronic constipation	x						x		5-HT4 agonists (prucalopride, velusetrag, naronapride) versus placebo or active control		x		13	2013
Suares 2011[4]	chronic idiopathic or functional constipation	x					x			fibre versus placebo or no treatment		x		6	2010
Belsey 2010[12]	non-organic constipation[a]	x				x				PEG versus placebo or active comparator		x		20	2009
Ford 2010[13]	chronic idiopathic constipation	x				x		x	x	osmotic or stimulant laxatives or pharmacologic agents (prucalopride, lubiprostone or linaclotide) versus placebo		x		21	2010

Author, year	Population	Adults	Children	Interventions	Stool softeners	Laxatives	Bulking agents	5-HT4 agonists	Other	Treatment comparisons	Study designs	RCTs	Other designs	Total studies included	Literature search date
Constipation associated with other disorders or conditions															
Turawa 2014[14]	postpartum constipation	x			x	x	x		x	laxatives, surgery, educational or behavioral interventions versus placebo, no treatment, or another intervention,		x		0	2014
Ford 2013[15]	opioid induced constipation	x						x	x	prucalopride, methylnaltrexone, naloxone, alvimopan, lubiprostone, linaclotide compared with each other or placebo		x		17	2012
Ruston 2013[6]	opioid induced constipation	x			x	x				PEG versus lactulose, docusate sodium or sennosides		x		0	2012
Candy 2011[16]	palliative care	x				x			x	laxatives or methylnaltrexone versus placebo or another treatment		x		7	2010
Coggrave 2014[3]	patients with central neurological diseases and fecal incontinence or constipation	x			x	x	x	x	x	conservative management (diet, oral drug or rectal evacuation therapy, bowel training program, and assistive techniques), or surgical measures versus placebo, no treatment or active comparators		x	x	21	2012

[a]Included patients with secondary constipation (e.g., opioid induced, Parkinson's disease) but excluded those with primary bowel disease induced constipation (e.g. irritable bowel syndrome, Hirschsprung's disease).

APPENDIX 3: Critical Appraisal

Author, year	Strengths	Limitations
Chen 2014[9] Childhood chronic or functional constipation	• Inclusion criteria clearly defined • Comprehensive literature search of multiple databases • Two researchers selected, appraised and extracted data • Validity assessed using the Delphi list • Risk of publication bias assessed • Authors report no conflicts of interest	• Excluded non-English studies
Gordon 2012[5] Childhood functional constipation	• Inclusion criteria clearly defined • Comprehensive literature search of multiple databases • Two researchers selected, appraised and extracted data • Validity assessed using Cochrane risk of bias tool	• No systematic search for unpublished studies • No conflict of interest statement
Lee Robichaud 2010[10] Chronic constipation	• Inclusion criteria clearly defined • Comprehensive literature search of multiple databases • Two researchers selected, appraised and extracted data • Validity assessed using Cochrane risk of bias tool • Risk of publication bias assessed	• No systematic search for unpublished studies • No conflict of interest statement • No assessment of AE associated with treatment
Shin 2014[11] Chronic constipation	• Inclusion criteria clearly defined • Comprehensive literature search of multiple databases • Two researchers selected, appraised and extracted data • Validity assessed using Cochrane risk of bias tool	• No systematic search for unpublished studies • No assessment of publication bias • Authors have potential conflicts of interest
Suares 2011[4] Chronic idiopathic constipation	• Inclusion criteria clearly defined • Comprehensive literature search of multiple databases • Two researchers selected, appraised and extracted data • Validity assessed using Cochrane risk of bias tool • Authors report no conflicts of interest	• No systematic search for unpublished studies • No assessment of publication bias

Author, year	Strengths	Limitations
Belsey 2010[12] Non-organic constipation	• Inclusion criteria clearly defined • Comprehensive literature search of multiple databases • Two researchers appraised and extracted data • Validity assessed using Jadad criteria	• Excluded unpublished studies • Unclear if two reviewers independently screened and extracted articles • No assessment of publication bias • Industry funded
Ford 2010[13] Chronic idiopathic constipation	• Inclusion criteria clearly defined • Comprehensive literature search of multiple databases • Two researchers selected, appraised and extracted data • Validity assessed using Cochrane risk of bias tool • Risk of publication bias assessed • Authors report no conflicts of interest	• No systematic search for unpublished studies
Turawa 2014[14] Postpartum constipation	• Inclusion criteria clearly defined • Comprehensive literature search of multiple databases • Two researchers screened studies for inclusion in the systematic review (no studies met the inclusion criteria)	• No conflict of interest statement
Ford 2013[15] Opioid-induced constipation	• Inclusion criteria clearly defined • Comprehensive literature search of multiple databases • Two researchers selected, appraised and extracted data • Validity assessed using Cochrane risk of bias tool • Publication bias assessed • Authors report no conflicts of interest	• No major limitations identified
Ruston 2013[6] Opioid-induced constipation	• Inclusion criteria clearly defined • Comprehensive literature search of multiple databases and grey literature • Two researchers screened studies for inclusion in the systematic review (no studies met the inclusion criteria)	• Authors have potential conflicts of interest

Author, year	Strengths	Limitations
Candy 2011[16] Palliative care	• Inclusion criteria clearly defined • Comprehensive literature search of multiple databases and grey literature • Two researchers selected, appraised and extracted data • Validity assessed using Cochrane risk of bias tool • Risk of publication bias assessed	• Partial industry funding
Coggrave 2014[3] Central neurologic dieases	• Inclusion criteria clearly defined • Comprehensive literature search of multiple databases • Two researchers selected, appraised and extracted data • Risk of bias was assessed for randomization, allocation concealment, and blinding methods, and for incomplete outcome data reporting	• No systematic search for unpublished studies • No assessment of publication bias • No conflict of interest statement

APPENDIX 4: Summary of Findings

Table 2. Stool frequency: Comparison with placebo or no treatment

Author, year, population	Treatment comparison	Number of stools per week[a]	N trials, I^2, [GRADE rating][bc]
Children			
Gordon 2012[5] Childhood functional constipation	PEG versus placebo	MD 2.61; 95% CI, 1.15 to 4.08	2 RCTs, I^2 = 58% [low quality evidence]
Adults			
Ford 2010[13] Chronic idiopathic constipation	Laxatives versus placebo	MD 2.55; 95% CI, 1.53 to 3.57	6 RCTs, I^2 = 100%
Suares 2011[4] Chronic idiopathic constipation	Psyllium versus placebo	Improvement of 0.9 more stools per week with psyllium after 8 weeks compared with no change in placebo group, P < 0.05	1 RCT
Shin 2014[11] Chronic constipation	5-HT4 agonists versus placebo or PEG[d]	Proportion who achieved mean of ≥3 SCBM per week: RR 1.85; 95% CI, 1.23, 2.79 Proportion with mean improvement of ≥1 SCBM per week from baseline: RR 1.57; 95% CI, 1.19, 2.06	11 RCTs, I^2 = 89% 11 RCTs, I^2 = 89%
Belsey 2010[12] Non-organic constipation	PEG versus placebo	MD 1.98; 95% CI, 1.16 to 2.81	10 RCTs, I^2 = 82%

Author, year, population	Treatment comparison	Number of stools per week[a]	N trials, I^2, [GRADE rating][bc]
Ford 2013[15] Opioid-induced constipation	Prucalopride versus placebo	Proportion of patients with an increase ≥1 SCBM per week Prucalopride 2 mg/day: 35% Prucalopride 4 mg/day: 39% Placebo: 23% No statistically significant difference between groups	1 RCT
Coggrave 2014[3] Central neurologic dieases	Psyllium versus placebo	MD 2.20; 95% CI, 1.40 to 3.00 [d]	1 RCT
	Macrogol electrolyte solution versus placebo	MD 2.90; 95% CI, 1.48 to 4.32	1 RCT
	Prucalopride versus placebo	Statistically significant median increase in weekly bowel movements (0.6; 95% CI, 0.2 to 1.2) from baseline to 4 weeks, for prucalopride 2 mg/day group in 23 patients with spinal cord injury. No data on placebo group were reported.	1 RCT
Turawa 2014[14] Postpartum constipations	Laxatives, stool softeners or bulking agents versus placebo or no treatment	No data available	0 RCTs

CI = confidence interval; MD = mean difference; PEG = polyethylene glycol; RCT = randomized controlled trial; SCBM = spontaneous complete bowel movements
[a]Unlesss otherwise stated, the data reported are the mean differences between treatment and placebo groups on the number of stools per week. A mean difference with lower and upper confidence intervals that exceed 0 shows that the treatment was statistically signficantly superior to the control.
[b]The GRADE rating of the overall quality of evidence was reported in some systematic reviews and have been abstracted where available.
[c]I^2 is a measure of statistical heterogeneity and represents the proportion of the variability in the study estimates that is due to differences between studies.
[c]One RCT compared an 5-HT4 agonist to PEG; all other studies were placebo controlled.
[d]Bowel motions per week.

Table 3: Stool frequency: Active comparator

Author, year, population	Treatment comparison	Number of stools per week [a]	N trials, I^2, [GRADE rating][b]
Children			
Chen 2014[9] Childhood chronic or functional constipation	PEG versus non-PEG laxatives	Change from baseline: MD 0.38; 95% CI, -0.11 to 0.87	7 RCTs, I^2 = 89%
Gordon 2012[5] Childhood functional constipation	PEG versus lactulose	MD 1.09; 95% CI, 0.02 to 2.17	4 RCTs, I^2 = 70% [very low quality evidence]
	PEG versus milk of magnesia	MD 0.69; 95% CI, 0.48 to 0.89	3 RCTs, I^2 = 0% [low quality evidence]
	PEG versus liquid paraffin	No significant difference detected in 1 RCT MD 0.70; 95% CI, -0.38 to 1.78 Second RCT reported PEG patients had more frequent bowel movements, P < 0.005	2 RCTs
	PEG versus enemas	MD 1.00; 95% CI, -1.58 to 3.58	1 RCT
	Dietary fibre mix versus lactulose	Mean stools per week: Fibre: 7; lactulose: 6 P = 0.48	1 RCT
	Senna versus lactulose	No statistically significant difference between groups	1 RCT
	Lactitol versus lactulose	MD -0.80; 95% CI, -2.63 to 1.03	1 RCT
	Liquid paraffin versus lactulose	MD 4.94; 95% CI, 4.28 to 5.61	2 RCTs, I^2 = 0% [low quality evidence]

Author, year, population	Treatment comparison	Number of stools per week [a]	N trials, I^2, [GRADE rating][b]
Children and Adults			
Lee Robichaud 2010[10] Chronic constipation	PEG versus lactulose	Pooled data: MD 0.65; 95% CI, 0.15 to 1.15 Two of four RCTs with data not suitable for meta-analysis reported stool frequency was higher with PEG than lactulose.	5 RCTs, I^2 = 77%
Adults			
Belsey 2010[12] Non-organic constipation	PEG versus lactulose	MD 1.01; 95% CI, 0.41 to 1.62	7 RCTs, I^2 = 54%
	PEG versus ispaghula	Two RCTs reported statistically significant benefits in weekly defication rates for PEG over ispaghula. Mean differences between groups were 2.78 (P <0.001) and 1.09 (P <0.05) stools per week.	2 RCTs
	PEG with electrolytes versus PEG without electrolytes	PEG without electrolytes was non-inferior to PEG with electrolytes in terms of mean number of stools per week. Ratio of stool frequency 0.9; 95% CI, 0.74 to 1.10)	1 RCT
Candy 2011[16] Palliative care	Magnesium hydroxide plus liquid paraffin versus senna plus lactulose	No statistically significant difference between groups in stool frequency. 19/35 (54%) of patients had normal bowel function.	1 RCT
	Senna versus lactulose	No statistical difference in defecation-free periods and the mean number of defecation days (senna 8.9 days; lactulose 10.6 days).	1 RCT
Ruston 2013[6] Opioid-induced constipation	PEG versus lactulose, docusate sodium or sennosides	No data available	0 RCTs

Author, year, population	Treatment comparison	Number of stools per week [a]	N trials, I^2, [GRADE rating][b]
Turawa 2014[14] Postpartum constipations	Laxatives, stool softeners or bulking agents versus another intervention	No data available	0 RCTs

CI = confidence interval; MD = mean difference; PEG = polyethylene glycol; RCT = randomized controlled trial

[a]Unlesss otherwise stated, the data reported are the mean differences between treatment and control groups on the number of stools per week. A mean difference with lower and upper confidence intervals that exceed 0 shows that the treatment was statistically signficantly superior to the control.

[b]The GRADE rating of the overall quality of evidence was reported in some systematic reviews and have been abstracted where available.

Table 4: Other efficacy outcomes

Author, year, population	Treatment comparison	Outcome	Results	N trials, I^2
Placebo				
Adults				
Ford 2010[13] Chronic idiopathic constipation	Laxatives versus placebo	Failed to respond to therapy	RR 0.52; 95% CI, 0.46 to 0.60	7 RCTs, I^2 = 42%
	Prucalopride versus placebo	Failed to respond to therapy	RR 0.82; 95% CI, 0.76 to 0.88	7 RCTs, I^2 = 60%
Suares 2011[4] Chronic idiopathic constipation	Psyllium versus placebo	Normalization of evacuation	Psyllium: 87%, placebo: 30%, P < 0.001	2 RCTs
		Constipation related symptoms	Statistically significant improvement in constipation-related sypmtoms for 87% of patients who received psyllium versus placebo (47%), P < 0.001.	
Shin 2014[11] Chronic constipation	5-HT4 agonists versus placebo or PEG	Proportion of patients with increase of ≥1 point in PAC-QOL[a] satisfaction score	RR 1.51; 95% CI, 1.07 to 2.11	6 RCTs, I^2 = 91 %
		Proportion of patients with increase of ≥1 point in PAC-SYM[b] score	RR 1.47; 95% CI, 1.10 to 1.98	6 RCTs, I^2 = 83%
Coggrave 2014[3] Central neurologic dieases	Prucalopride versus placebo	Improvement in constipation	One RCT (abstract, 11 MS patients) reported the severity of constipation improved with prucalopride 1 mg and 2 mg doses.	1 RCT
	Macrogol electrolyte solution versus placebo	Failed to respond to therapy	RR 0.29; 95% CI, 0.11 to 0.72	1 RCT

Author, year, population	Treatment comparison	Outcome	Results	N trials, I^2
Active comparator				
Children				
Chen 2014[9] Childhood functional constipation	PEG versus non-PEG laxatives	Successful disimpaction	Week 4: OR 1.63; 95% CI, 1.09 to 2.44 Week 12: OR 1.87; 95% CI, 1.03 to 3.37	7 RCTs, 24% 3 RCTs, I^2 = 9%
Gordon 2012[5] Childhood functional constipation	PEG versus lactulose	Need for additional therapy	PEG: 18%, Lactulose: 30% OR 0.49, 95% CI, 0.27 to 0.89	3 RCTs, I^2 = 48%
	PEG versus enemas	Successful disimpaction	PEG: 68%, enema: 80% OR 0.52, 95% CI, 0.20 to 1.37	1 RCT
Children and Adults				
Lee Robichaud 2010[10] Chronic constipation	PEG versus lactulose	Need for additional therapy	OR 0.25; 95% CI, 0.13 to 0.50	3 RCTs, I^2 = 9%

CI = confidence interval; MS = Multipls Sclerosis; OR = odds ratio; PAC-QOL = Patient Assessment of Constipation Quality of Life questionnaire; PAC-SYM = Patient Assessment of Constipation Symptoms; PEG = polyethylene glycol; RCT = randomized controlled trial; RR = relative risk;

[a]PAC-QOL is a self-reported questionnaire with four domains (physical discomfort, psychosocial discomfort, worries and concerns, and satisfation) related to the effects of constipation on their daily lives. Scores range from 0 to 4 with lower scores indicating better quality of life. In the review by Shin et al.,[11] an increase in at least one point on the overall score was chosen as a clinically important difference.

[b]PAC-SYM provides data on 12 constipation related symptoms scored on 3 subscales (stool, abdominal, or rectal symptoms). Scores range from 0 (no symptoms) to 4 (very severe symptoms). Shin et al.[11] state that the questionnaire is validated, and is reproducible and responsive to change.

Table 5: Adverse events

Author, year, population	Treatment comparison	Adverse events	SAE
Comparision with Placebo			
Children			
Gordon 2012[5] Childhood functional constipation	PEG versus placebo	Incidence of AE similar between groups. AE reported: flatulence, abdominal pain, nausea, diarrhea, headache	PEG: 0% Placebo: 8% No statistically significant difference between groups
Adults			
Ford 2010[13] Chronic idiopathic constipation	Laxatives versus placebo	Laxatives associated with higher risk of any AE (RR 1.94; 95% CI, 1.52 to 2.47; 1 RCT), or diarrhea (RR 13.75; 95% CI, 2.82 to 67.14; 2 RCTs), but not abdominal pain or headache, versus placebo.	NR
	Prucalopride versus placebo	Prucalopride associated with higher risk of any AE (RR 1.14; 95% CI, 1.05 to 1.24; 6 RCTs), headache, nausea or diarrhea than placebo.	No increased risk of SAE (RR 0.88; 95% CI, 0.58 to 1.34)
Suares 2011[4] Chronic idiopathic constipation	Psyllium versus placebo	One RCT reported abdominal pain in 18% of patients on psyllium versus 0% on placebo. The rate of back pain, bloating or cramping was similar between groups. A second RCT reported similar number of patients stopping treatment due to adverse events.	NR
Shin 2014[11] Chronic constipation	5-HT4 agonists versus placebo or PEG	Any AE: RR 1.25; 95% CI, 1.14 to 1.38 [12 RCTs, I^2 = 60%] The incidence of headache, diarrhea, nausea and abdominal pain were statistically significantly higher in 5-HT4 agonist versus control groups.	NR

Author, year, population	Treatment comparison	Adverse events	SAE
Belsey 2010[12] Non-organic constipation	PEG versus placebo	Three RCTs reported similar incidence of AE. Three trials reported more diarrhea, 1 reported more gas or cramps, and 1 reported more gastrointestinal complaints with PEG versus placebo.	In 1 RCT, 2 cases of severe diarrhea with PEG were reported. No other SAE reported.
Ford 2013[15] Opioid-induced constipation	Prucalopride versus placebo	In one RCT, 52% of all particpants experienced an AE. The incidence of diarrha, nausea, vomiting, headache and global pain was similar between groups. Abdominal pain occurred more frequently among those who received 4 mg prucalopride daily.	NR
Coggrave 2014[3] Central neurologic dieases	Prucalopride versus placebo	In one RCT, 81% of patients on prucalopride reported mild to moderate AE, including flatulence, diarrhea, abdominal pain. No data presented for patients on placebo. 22% discontinued treatment due to AE. A second RCT reported diarrhea as an AE but provided no data on the incidence.	NR
Active comparators			
Children			
Chen 2014[9] Childhood functional constipation	PEG versus non-PEG laxatives	AE reported: diarrhea, abdominal pain, nausea, vomiting, pain at defecation, straining at defecation, bloating or flatulence, hard stool consistency, bad palatability, rectal bleeding.	NR
Gordon 2012[5] Childhood functional constipation	PEG versus lactulose	Any AE: PEG: 24%, lactulose: 37% OR 0.37; 95% CI 0.14 to 1.03; 2 RCTs	NR
	PEG versus milk of magnesia	Diarrhea PEG: 4%, milk of magnesia: 28%, P = 0.002; 1 RCT	PEG: 1 SAE (allergy), milk of magnesia: no events
	PEG versus enemas	Higher incidence of fecal incontinenece and watery stool with PEG (no details reported).	NR

Author, year, population	Treatment comparison	Adverse events	SAE
	PEG versus liquid paraffin	Higher incidence of vomiting with PEG than lactulose (P <0.005) in 1 RCTs	No SAEs reported
	Liquid paraffin versus lactulose	Abdominal pain, distention and watery stools reported	No SAEs reported
	Dietary fibre versus lactulose	Diarrhea Fibre: 1 case, lactulose: 2 cases	No SAEs reported
	Senna versus lactulose	Minor AE of colic and diarrhea more common in senna group	No SAEs reported
Adults			
Belsey 2010[12] Non-organic constipation	PEG versus lactulose	Incidence of AE PEG: 6% to 16%, lactulose: 10% to 24% WDAE PEG: 0% to 9%, lactulose: 0% to 10% One study reported statistically significantly more liquid stools with PEG versus lactulose during first 2 weeks of therapy.	No SAE reported.
	PEG versus ispaghula	Incidence of AE PEG: 8% to 12%, ispaghula: 8% to 12% WDAE were low and similar between groups in the two RCTs.	NR
	PEG with electrolytes versus PEG without electrolytes	Incidence of AE PEG with electrolytes: 19% PEG without electrolytes: 23%	NR
Candy 2011[16] Palliative care	Magnesium hydroxide plus liquid paraffin versus senna plus lactulose	In one RCT, 1 patient in each group found treatment intolerably nauseating. 1 patient in senna plus lactulose had gripping abdominal pain.	NR
	Senna versus lactulose	In one RCT, 3 patients per group reported diarrhea, vomiting and cramps. The number of patients who withdrew from the study were similar between groups.	NR

AE = adverse events; CI = confidence interval; NR = not reported; OR = odds ratio; PEG = polyethylene glycol; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse events; WDAE = withdrawals due to adverse events

APPENDIX 5: Additional articles of potential interest

This appendix includes review articles that did not meet the criteria to be a systematic review, or provided insuffienct detail to determine the methods used when conducting the review.

Canadian Agency for Drugs and Technologies in Health. Dioctyl sulfosuccinate or docusate (calcium or sodium) for the prevention or management of constipation: a review of the clinical effectiveness [Internet]. Ottawa: The Agency; 2014 Jun 26. (Rapid Response Report: Summary with Critical Appraisal). [cited 2014 Nov 13]. Available from: http://www.cadth.ca/media/pdf/htis/jul-2014/RC0561%20Stool%20Softeners%20Final.pdf

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